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EXAMINER	
GOLDBERG, J	
ART UNIT	**PAPER NUMBER**
1655	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/613,887	HOGAN, KIRK	
	Examiner	Art Unit	
	Jeanine A Enewold Goldberg	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3, 6, 7.
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed March 26, 2001. Currently, claims 1-20 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

2. Any objections and rejections not reiterated below are hereby withdrawn.

3. This action contains new grounds of rejection necessitated by amendment.

Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The essential elements of the claims are drawn to a method for selecting an operative course of action by detecting two or more genetic markers.

The specification teaches only a hand-full of mutations within ten different genes which have been identified as having any effect on the response to anesthesia. The

specification provides four tables which illustrate the mutations in the specified genes and the percent of incidences.

There is not adequate description of the genus of genetic markers which may be used to screen for a patient's response to anesthesia and related medication. The specification only discloses ten genes associated with poor response to anesthesia. Further, within these ten genes only twenty specific mutations within the scope of the genus: genetic markers which may be used to screen for a patient's response to anesthesia and related medication. The general knowledge in the art concerning genetic markers which may be used to screen for a patient's response to anesthesia and related medication does not provide any indication of how to readily identify these genetic markers. The twenty mutations described are not representative of the genus of genetic markers which may be used to screen for a patient's response to anesthesia and related medication. There is substantial variability among the species of nucleic acids encompassed in the scope of the claim because only twenty specific mutations have been identified. The specification has also not defined a structural feature of the genetic markers which may be used to screen for a patient's response to anesthesia and related medication which would be common to all members of the genus that constitutes a substantial portion of the genus. Furthermore, one of skill in the art would conclude that applicant was not in possession of the claimed "genetic markers which may be used to screen for a patient's response to anesthesia and related medication" because the description of only twenty members of this genus is not representative of the variants of the genus and is insufficient to support the claims. Thus, the

specification does not adequately provide a written description for genetic markers which may be used to screen for a patient's response to anesthesia and related medication.

Response to Arguments

The response traverses the rejection.

The response asserts that the claims are directed to methods, not a composition of matter. This argument has been reviewed but is not convincing because the methods of the instant claims require compositions which "are useful in selecting a perioperative course of action, namely anesthesia". The claims are to a method of making a map for use in selecting perioperative course of action. In order to have utility, the markers used to make the genome profile must be associated with patient's response to such action. Consequently, the specification must establish that a representative number of genetic markers are associated with such as response. The specific example that the response asserts is not an analogous method since the method of "databasing and displaying sequence information" do not require a composition with any intended use.

The response asserts that there is adequate description of the genus of markers. This argument has been reviewed but is not convincing because the specification does not teach a representative number of markers from the genus of genetic markers which may be used to screen for a patient's response to anesthesia and related medication. The response points to the specification sections I.B. and I.C. on pages 27 and 29 for support. Page 27 of the specification broadly suggests using genetic markers which are

"selected for the preioperative genomic profile that are tailored towards a specific medical or surgical procedure. The specification does not provide any specific criteria for markers which are specific to anesthesia. The specification alternatively broadly discusses detection of markers. Page 29 of the specification is directed to categories of markers. Similarly, the specification broadly teaches markers which have diagnostic utility, however, the specification does not specifically define any of these markers by name. Claims 2-7, 18-19 are directed to anesthesia. Pages 27 and 29 do not teach polymorphisms which are related to response to anesthesia. The description provides methods to search for the genetic markers, but not the markers which are associated with the course of action, namely anesthesia. These teachings in the specification are not support for the broadly claimed use of markers for generatinc a genomic profile for use in selecting a perioperative course of action because the specification fails to teach a representative number of makers which are associated with anesthesia.

The response asserts that a common structural feature is not claimed. This argument has been reviewed but is not convincing because as stated above, the claims are directed to a method which requires a composition which must meet the description guidelines. Thus, a common structural feature must be defined to provide adequate written description of the claimed genus of genetic markers which are useful in selecting a perioperative course of action.

The response asserts the specification identifies the incorporated markers. This argument has been reviewed but is not convincing because the specification only teaches 20 markers which are associated with various conditions. The specification

does not provide any specific guidance to determining which markers can and can not be used in perioperative use. The pages 27-30 of the instant specification are not specific to detecting anesthesia or other perioperative markers.

The response asserts that the examples give support to the genus. This argument has been reviewed but is not convincing because the claims are broadly drawn to detecting two (any two) genetic markers to generate a genomic profile for use in selecting a perioperative course of action. This encompasses any SNP, deletion, translocation, expansion, insertion in any gene which has been identified or is yet to be identified. The response asserts that the instant markers are only examples. However, the art and the specification must provide an adequate description of a representative number of genetic markers within the scope of the invention. There is no evidence that other mutation or makers are correlated to anesthesia or other perioperative courses of action.

In conclusion, the specification teaches alterations which are associated with Butyrylcholinesterase deficiency, poor debrisiquine metabolism, thrombus, and malignant hyperthermia. The specification and the art support the assertion that "MH is an autosomal dominant trait that causes a severe, uncontrollable fever when anesthesia is administered" (pg 1, lines 25-27). The other conditions do not appear to be as closely associated with anesthesia. The specification states "muscle relaxants commonly given in conjunction with anesthesia, can cause prolonged paralysis and apnea in a patient after the patient has awoken from anesthesia" (pg 2, lines 8-10). Moreover, the specification teaches that "mutations in BchE can also lead to delayed metabolism and

possible toxicity when ester local anesthetics are used" (pg 2, lines 11-12). The specification teaches that mutations in "cytochrome P450 enzymes, which metabolize a variety of drugs commonly given in conjunction with surgical procedures, can have adverse reactions due either to the inability to activate or metabolize certain drugs (morphine derivatives and anti-dysrrhthmics)"(pg 2, lines 17-20). The specification teaches that TNF2 allele of the TNFalpha gene have an increased susceptibility to sepsis and death from sepsis after surgery. The specification supports that not all markers are associated with anesthesia. Based upon the teachings in the specification only these markers in RYR1 and CACNA1S and CPT2 may be associated directly with anesthesia. The specification fails to teach a representative number of genetic markers which are associated with anesthesia.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting Butyrylcholinesterase deficiency, poor debrisiquine metabolism, thrombus, and malignant hyperthermia based upon the detection of two or more genetic markers for use in generating a genomic

profile which is used in selecting an operative course of action, does not reasonably provide enablement for detecting **any** two genetic markers and generating a profile for use in selecting **any** operative course of action. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are broadly drawn to providing a sample from a perioperative subject and detecting two or more genetic markers to generate a genomic profile for use in selecting an operative course of action.

The specification teaches ten distinct genes (namely, BCE, CYP2D6, MTHFR, MS, CBS, F 5 Leiden, Prothrombin, RYR1, CACNA1S and CPT 2) which contain 20 different mutations, as set forth in Tables 1-4, which may be used to detect possible response to anesthesia. The specification teaches mutations in the ten identified genes as being associated with Butyrylcholinesterase deficiency, poor debrisiquine metabolism, thrombus, and malignant hyperthermia (pg. 48-49). The specification provides an extensive list of hyperlinks which provide sequence data for numerous markers (pg. 26-27). The specification teaches alterations which are associated with Butyrylcholinesterase deficiency, poor debrisiquine metabolism, thrombus, and malignant hyperthermia. The specification and the art support that "MH is an autosomal dominant trait that causes a severe, uncontrollable fever when anesthesia is administered" (pg 1, lines 25-27). The other conditions do not appear to be as closely associated with anesthesia. The specification states "muscle relaxants commonly given in conjunction with anesthesia, can cause prolonged paralysis and apnea in a patient

after the patient has awoken from anesthesia" (pg 2, lines 8-10). Moreover, the specification teaches that "mutations in BchE can also lead to delayed metabolism and possible toxicity when ester local anesthetics are used" (pg 2, lines 11-12). The specification teaches that mutations in "cytochrome P450 enzymes, which metabolize a variety of drugs commonly given in conjunction with surgical procedures, can have adverse reactions due either to the inability to activate or metabolize certain drugs (morphine derivatives and anti-dysrrhthmics)"(pg 2, lines 17-20). The specification teaches that TNF2 allele of the TNFalpha gene have an increased susceptibility to sepsis and death from sepsis after surgery.

The art teaches malignant hyperthermia (MH) is a pharmacogenetic disease with autosomal dominant inheritance triggered by exposure to commonly used inhalational anesthetics (Sudbrak et al. Human Mol. Genetics, Vol. 2, No. 7, pg. 857-862, 1993). Sudbrak excludes several loci which do not give support for a MH susceptibly locus. O'Brien et al (J. Med. Genet. Vol. 32, No. 11, pg. 913-914, 1995) teaches that Arg163Cys substitution in the RYR1 gene does not cosegregate with MH susceptibility (abstract). Moreover, O'Brien teaches that DHPR is unlikely to be a major cause of MH. Tsai et al (Am. J. Hum. Genet. Vol. 59, pg. 1262-1267, 1996) teaches that an insertion in the CBS gene seems to affect the activity of the CBS enzymes, the prevalence is somewhat increase in patients with premature coronary-artery disease, although not statistically significant. Hecht et al (Anesth. Analg, Vol. 84, pg. 461-464, 1997) teaches a G1583A mutation in CACNL1A3 which is associated with HypoPP. Hecht also teaches that HypoPP has been identified as a disorder that can predispose a patient to

the syndrome of MH which the risk of triggering skeletal muscle contraction and rhabdomyolysis, together with earlier reports of flaccid paralysis aggravated by surgery and general anesthesia, appear to favor regional anesthesia in this population whenever feasible (abstract). Hecht also teaches that MH susceptibility associated with HypoPP and of hypokalemia elicited by regional anesthesia suggests that hybrid anesthetic techniques be avoided (pg. 462, col. 2). Sachse et al (Am. J. Hum. Genet. Vol. 60, pg. 284-295, 1997) teaches that therapeutic efficacy and adverse events in treatment with many drugs depend on CYP2D6 activity, genotyping CYP2D6 may become a routine part of an individually optimized drug treatment (p 284, col. 2). Korte et al (Clin. Chem. Lab. Med, Vol. 36, No. 4, pg. 235-240, 1998) teaches to establish a possible "perioperative reference range" for thrombin generation prothrombin fragment F1+2 and fibrin degradation markers were measured (abstract). Korte also teaches that preoperative determination of molecular markers would be helpful in identifying a group of patients at high risk for intraoperative disorder of hemostasis by exclusion of low risk patients (abstract). As seen in Table 2 and Table 3, the results of the detection assay for the two genetic markers were observed (pg. 237).

Hogan (Current Opinion in Neurology, Vol. 11, pg. 469-476, 1998) teaches several mutant alleles at loci on chromosome 1q, 3q, 5p, 7q and 19q which account for up to 50% of MH susceptibility (abstract). Hogan proposes preoperative genotyping for panels of MHS alleles would benefit by selection of an alternate anesthetic (pg. 474, col. 1). Hogan extensively discusses the unpredictability in the RYR1 gene mutations and the relation to MH. Hogan teaches up to 17 mutations in the RYR1 gene have been

identified (pg 471, col 1). "Most putative MH mutations are orphans appearing in single families, frequently in association with central core disease. Mutation analysis is rarely commensurate with IVCT results in full" (pg 471, col 1). Hogan further states that "when an identical mutation has arisen in more than an isolated pedigree, the correlation varies from family to family" (pg 471 col 1). Further, Hogan teaches that "whether these observations are best explained by inaccurate diagnosis on the basis of the IVCT, lack of a causal relation between candidate polymorphisms and the malignant hyperthermia phenotype, or the possibility of two or more malignant hyperthermia-associated muations acting alone or in concert but segregating within a single pedigree, has not been answered" (pg 471, col 2). Hogan explicitly states that "until very nearly all muations in all predisposing genes are charted, the causality for each is unambiguous, offering family genotyping for purposes other than research will be premature" (pg 474, col 1). Hogan teaches that "patients lacking the mutant alleles sought may not be clear of risk (pg 473, col 2).

Brandt et al (Hum. Mol. Genetics, Vol 8, No. 11, pg 2055-2062, 1999) teaches screening of approximately 105 MH families for mutations. Despite the extensive number of known mutations in RYR1, "interpretation must be performed with care because lack of the particular mutation segregating in the family does not exclude absence of further independent unknown mutations. Additionally, genetic screening is not yet suitable for routine diagnostics due to the low incidence of each mutation and the vastness of the gene" (pg 2058, col 2). De Stefano et al (New England J. Med, Vol 341, pg 801-806, 1999) teaches screening for two point mutations, one in F 5 Leiden

and one in the prothrombin gene which are the most common causes of inherited thrombophilia. Thus, carriers of both of these mutations have an increased risk of recurrent deep venous thrombosis after a first episode and are candidates for lifelong anticoagulation.

Based upon the teachings in the specification and the art, the skilled artisan would be unable to practice the invention as broadly as claimed. First, the specification only provides twenty mutations which have association with "selection an operative course of action". It would be undue experimentation for the skilled artisan to study the voluminous known mutations and determine association with anesthesia and medical complications. Limiting the scope of the claims to recite the ten genes would still require undue experimentation for the skilled artisan to evaluate the large number of known mutations in these genes and determine the association with anesthesia complications.

Secondly, the specification only contemplates butyrylcholinesterase deficiency, poor debrisiquine metabolism, thrombus, and malignant hyperthermia (pg. 48-49). The specification does not provide genetic markers for use in selecting **any** operative course of action. The specification does not teach any specific combination of markers and what the appropriate "operative course of action" entails. It would require undue experimentation for the skilled artisan to minimally take the 20 mutations provided in the specification and determine appropriate courses of action for all of the various combinations if detected. Such combinations would include all of the different pairs of mutations, all of the different triples of mutations and so forth. The skilled artisan would

be required to identify subjects which had all of the combinations and determine what the "operative course of action" would be for any scenario which is unreasonable. Furthermore, the specification does not provide any guidance as to how to select the specific anesthesia based solely upon these markers and their correlation to an invasive versus non-invasive procedure. The specification provides no distinction between genetic markers which are useful in general anesthesia versus region anesthesia. It is unclear whether these markers have the same effect in determining complications for each type of anesthesia or whether different markers has different effects. The specification does not appear to provide any distinction between different types of anesthesia and their association with different mutations. It is unpredictable for the skilled artisan to determine which of the provided mutations would have complications with specific anethestics. The specification does not teach how different types of surgery are associated with the genetic markers, i.e. non-invasive and invasive surgery. It is unclear how the skilled artisan would differentiate the information obtained from the genomic profile for obtaining information for non-invasive and invasive surgery since the specification does not provide any differentiation. While the claim is not particularly limited to these 20 mutations, the skilled artisan would be unable to practice the invention limited to this scope without undue experimentation.

Thirdly, based upon the teachings in the art, the detection of two genetic markers would not necessarily provide enough information to select an operative course of action appropriate for a particular patient. The art teaches "most putative MH mutations are orphans appearing in single families, frequently in association with central core

disease. Mutation analysis is rarely commensurate with IVCT results in full" (Hogan, pg 471, col 1). Hogan further states that "when an identical mutation has arisen in more than an isolated pedigree, the correlation varies from family to family" (pg 471 col 1). Hogan explicitly states that "until very nearly all mutations in all predisposing genes are charted, the causality for each is unambiguous, offering family genotyping for purposes other than research will be premature" (pg 474, col 1). Brandt teaches despite the extensive number of known mutations in RYR1, "interpretation must be performed with care because lack of the particular mutation segregating in the family does not exclude absence of further independent unknown mutations. Additionally, genetic screening is not yet suitable for routine diagnostics due to the low incidence of each mutation and the vastness of the gene" (pg 2058, col 2). Thus, the skilled artisan would expect unpredictability in assaying for two genetic markers and subsequently determining an appropriate course of action. It would unpredictable for the skilled artisan as taught by Hogan and Brandt.

Therefore, it would be undue experimentation for the skilled artisan to detect **any** genetic markers and infer an association between the makers and response to anesthesia based solely upon the guidance provided in the specification which teaches twenty mutations which are associated with Butyrylcholinesterase deficiency, poor debrisiquine metabolism, thrombus, and malignant hyperthermia, respectively (pg. 48-49).

Response to Arguments

The response traverses the rejection. The response asserts that the invention provides enablement for detecting any two genetic markers. This argument has been reviewed but is not convincing because the claim is directed to a method of generating a genomic profile for use in selecting a perioperative course of action. This method includes assaying for any two genetic markers. For example, the claim encompasses assaying for the t(12;16) which is the key genetic aberration in myxoid liposarcomas resulting in the fusion of the FUS gene in 16p11 and the CHOP gene in 12q13 and for the T(67)C mutation in the AGT gene which is a marker for predisposition for hypertiension. The specification provides no guidance how the genomic profile may be used in selecting a perioperative course of action. The claim broadly encompasses any two genetic markers in any gene or combination of genes in any organism (human, mouse, ape or lizard). The specification does not provide enablement for detecting any two genetic markers for use in selecting a perioperative course of action.

The response also asserts that the invention provides enablement for generating a profile for use in selecting a perioperative course of action. This argument has been reviewed but is not convincing because the claim encompasses any operative course of action. For example, the specification has not provide any guidance to the skilled artisan what perioperative course of action would be take provided that the translocation t(12;16) and the C mutation in the AGT gene were found.

The response asserts the specification teaches a genus of mutations of relevance in the perioperative interval. This argument has been reviewed but is not convincing because the response relies upon the "instructions in the present invention

in using the methods of the presently claimed invention". These "instructions" do not provide adequate guidance to the skilled artisan to determine which mutations or genetic markers would be suitable for "selecting a perioperative course of action". The criteria for selection of markers presented is very general and is not specifically applicable to anesthesia or pharmacokinetic risk. It is noted that "the knowledge of every marker sequence and mutation is not needed to practice the present invention" however a representative number of makers is required (as set forth in the Written Description Rejection above).

The response further asserts that the clinical validity and clinical utility of the mutaitions present as examples are well-established. The response also states that the "clinical validity and clinical utility of each of the alleles as taught in references presented by the Applicant as examples are not relavent to a non-enablement rejection for the reasons stated above." This argument has been reviewed but is not convincing because is it not clear which reasons "stated above" prove that the examples are not relavent to the enablement rejection. The references cited are pertinant to the enablement rejection. THe references have been used to suppport that it is unpredictable which mutations in which genes are association with anesthesia or other perioperative course of actions. The references teaches that mutations within genes generally accepted to be associated with anesthesia and perioperative courses of action are not associated. The response asserts that the statements of Hogan and Brandt "are irrelevant to the present invention since family screening is not claimed or specified, nor is family screening the problem which the present invention solves". The

claims are so broad that they encompass any family screening methods. The response fails to address all of Hogan. Hogan extensively discusses the unpredictability in the RYR1 gene mutations and the relation to MH. Hogan teaches up to 17 mutations in the RYR1 gene have been identified (pg 471, col 1). "Most putative MH mutations are orphans appearing in single families, frequently in association with central core disease. Mutation analysis is rarely commensurate with IVCT results in full" (pg 471, col 1). Hogan further states that "when an identical mutation has arisen in more than an isolated pedigree, the correlation varies from family to family" (pg 471 col 1). Further, Hogan teaches that "whether these observations are best explained by inaccurate diagnosis on the basis of the IVCT, lack of a causal relation between candidate polymorphisms and the malignant hyperthermia phenotype, or the possibility of two or more malignant hyperthermia-associated muations acting alone or in concert but segregating within a single pedigree, has not been answered" (pg 471, col 2). The art clearly teaches that genetic markers are unpredictably associated with perioperative courses of action.

The response asserts the skilled artisan requires no undue experimentation to evaluate which mutations are associated with anesthesia and medical complications. This argument has been reviewed but is not convincing because the specification has not clearly layed out which markers are associated with anesthesia and other medical conditions. The response asserts that I.B. and I.C. instruct precisely how the genus of relevant markers is identified. However, in order to determine whether markers meet the criteria is undue experimentation. For the skilled artisan to determine whether a

mutation in BRAC1 is associated with anethesia, the skilled artisan would be required to determine the analytical validity, clinical validity, clinical utility and commercial value. The specification provides no guidance as to how to assess these criteria and further does not provide whether a mutation in the BRAC1 gene meets these criteria. The association of a given marker and response to perioperative course of action, namely anesthesia, is highly unpredictable without evidence because, the specification nor the art provides any common structural or functional characteristics which would be apparent to the skilled artisan. Each marker of interest must be first validated to determine the relevance to a perioperative course of action, namely anethesia. Thus, the skilled artisan would be required to experimentally determine whether mutation A in the BRAC1 gene may be used in the genomic profile by sampling a population of "normal" and a population of "diseased" and determining whether the mutation A is associated with poor response to asthma. The specification has only provided 20 mutations which are associated with any conditions. Of these conditions, the specification teaches that MH is the only one associated with anesthesia. The other mutations provided do not directly affect anesthesia. The specification states "muscle relaxants commonly given in conjunction with anesthesia, can cause prolonged paralysis and apnea in a patient after the patient has awoken from anesthesia" (pg 2, lines 8-10). Moreover, the specification teaches that "mutations in BchE can also lead to delayed metabolism and possible toxicity when ester local anesthetics are used" (pg 2, lines 11-12). The specification teaches that mutations in "cytochrome P450 enzymes, which metabolize a variety of drugs commonly given in conjunction with

surgical procedures, can have adverse reactions due either to the inability to activate or metabolize certain drugs (morphine derivatives and anti-dysrrhthmics)"(pg 2, lines 17-20). The specification teaches that TNF2 allele of the TNFalpha gene have an increased susceptibility to sepsis and death from sepsis after surgery. These mutations are not associated with selecting administration of anesthesia during a surgical procedure.

The response asserts that the specificaiton teaches what an appropriate operative course of action entails. This argument has been reviewed but is not convincing because the claim does not require that "only mutations meeting explicit categorical criteria are included in the profile". The claim broadly recites "subjecting said sample to any assay for detecting two or more genetic markers to generate a genomic profile". This encompasses any two genetic markers. Experimentation is required of the skilled artisan to assess what course of action is selected since no prior information about the markers is required.

The response asserts that the invention does not claim to teach appropriate courses of action for all the various combinations if detected. This argument has been reviewed but is not convincing because the claims are broadly drawn to "subjecting said sample to any assay for detecting two or more genetic markers to generate a genomic profile for use in selecting a perioperative course of action". As previous posed, for example, the claim encompasses assaying for the t(12;16) which is the key genetic aberration in myxoid liposarcomas resulting in the fusion of the FUS gene in 16p11 and the CHOP gene in 12q13 and for the T(67)C mutation in the AGT gene which is a

marker for predisposition for hypertiension. The specification provides no guidance how the genomic profile may be used in selecting a perioperative course of action. The claim broadly encompasses any two genetic markers in any gene or combination of genes in any organism (human, mouse, ape or lizard). The specification does not provide enablement for detecting any two genetic markers for use in selecting a perioperative course of action.

The response asserts that the invention does not claim to provide guidance as to how to select the specific anesthesia based solely upon these markers. This argument has been reviewed but is not convincing because the response appears to be indicating that essential steps have been omitted from the method. The response states that the method of selecting a perioperative course of action is not possible based solely upon the identity of makers.

The response asserts that the specification does distinguish between different types of anesthesia and their association with different mutations. The response asserts that the invention does not claim that specific mutations are useful in general anesthesia while others are useful in regional anesthesia. This argument has been reviewed but is not convincing because Claims 3 and 4 are specifically drawn to these two embodiments. Claim 3 requires subjecting a sample to an assay for detecting two or more genetic markers for use in selecting general anesthesia. The specification has not provided any guidance as to whether general anesthesia should be selected given any combination or marker. Further, the claim is not limited to those markers presented in Table 1-4.

The response asserts that it is entirely predictable for the skilled artisan to determine which of the provided mutations would have complications with specific anesthetics. The response asserts that "to be considered for inclusion, every mutation should have predictable consequences, i.e. clinical validity. The skilled artisan therefore knows what complications are predictable, and which interventions to select by virtue of the tested mutations. This argument has been reviewed but is not convincing because the claim is broadly drawn to any number of mutations which have not been described nor enabled. The claim does not require using one of the "clinically valid" genetic markers. Thus, determining the "perioperative course of action" is unpredictable and requires undue experimentation.

The response asserts that the detection of two genetic markers provides enough information to select an operative course of action appropriate for a patient. The response asserts that two or more genetic markers may or may not determine a perioperative course depending on what the markers are and whether they are present or absent in a given patient. This argument has been reviewed but is not convincing because the claim is broadly directed to assaying for two markers to select a perioperative course of action. The response appears to be asserting that each patient should be considered carefully, since a specific allele will determine a course of action in some patients and not in others. This statement by the response supports the unpredictability of the markers. Since it is clear that a marker may determine a course of action in some patients and not in others, the markers do not act in a predictable manner such that a perioperative course of action may be selected given the detection

of two genetic markers. Moreover, it is unpredictable which patients the markers are informative in and which patients the markers are not informative in.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> **A person shall be entitled to a patent unless –**
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> **(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.**

6. Claims 1, 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Vogelstein (US Pat. 5,380,645, January 1995).

Vogelstein teaches a method for assessment of colorectal cancer by detecting genetic changes. Specifically, Vogelstein teaches a study in which allelic loss in patients was determined. For example, as seen in Table II, the first patient, as indicated by S7, was identified to have chromosomal arms on which allelic markers were lost for three distinct chromosomal arms. Thus, this perioperative subject, was subjected to an assay which identified two or more genetic markers, i.e. 7q, 18q and 20p, in which a

genetic profile was generated. This patient was thus grouped in Group II of the Vogelstein study which suggested that the patients were more likely to die with or from their cancer (col. 13, lines 1-5). Vogelstein also states "the measurement of allelic losses might help to identify patients with an otherwise relatively favorable prognosis who could benefit from additional therapy" (col. 13, lines 29-31).

Response to Arguments

The response traverses the rejection. The response asserts that Vogelstein does not teach "the assay generates a genomic profile for use in selecting a perioperative course of action". This argument has been reviewed but is not convincing because the individuals which are tested have undergone surgery to remove the tumor (col. 7) and the tumor is subjected to an assay which detects two or more genetic markers, namely 7q, 18q and 20p. This meets the limitations of the claimed invention since the profile may be inherently used for selecting a perioperative course of action.

Moreover, Vogelstein, however also teaches that those individuals with a high FAL groups could benefit from additional therapy. Thus, Vogelstein also teaches that the profile is useful in selecting whether additional therapy is useful.

Thus for the reasons above and those already of record, the rejection is maintained.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A1) Claim 1-20 are indefinite because the claims do not recite a positive process step which clearly relates back to the preamble. The preamble states that the method is for generating a genomic profile but the final process step is subjecting said sample to an assay for detecting two or more genetic markers to generate a genomic profile for use in selecting a perioperative course of action. Therefore the claims are unclear as to whether the method is a method of merely generating a genomic profile or generating a genomic profile for use in selecting a perioperative course of action. It is unclear what limitations, if any, the "for use" statement in the last line of the claim entails. With respect to Claim 17, the preamble states that the methods if a method for generating a genomic profile, however the final process step is subjecting said subject to a surgical procedure. Thus, the claim is unclear as to whether the method is a method for generating a genomic profile or a method of subjecting subjects to a surgical procedure.

Conclusion

8. No claims allowable.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
June 4, 2001

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP 1800 1600